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09/600,766	05/14/2001	Gary J. Nabel	UMV-1474US	1371

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EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/600,766	Applicant(s) NABEL ET AL.	
	Examiner David Guzo	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). ____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 10-14 are rejected under 35 U.S.C. 102(a) as being anticipated by Takada et al.

Applicants and Takada et al. (Cited by applicants, PNAS, Vol. 94, Dec. 1997, pp. 14764-14769, see whole article, particularly the Abstract and paragraphs 2, 4-5 of the "Results" section and the "Discussion" section) recite a genetic construct comprising a gene (green florescent protein, GFP) operably linked to a viral (VSV vector) carrier wherein the carrier is associated with a transmembrane glycoprotein of the Eboia virus and is expressed on the surface of the carrier and a method of targeting said gene to a cell comprising administering the genetic construct to the cell *ex vivo*. Takada et al. therefore teaches the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4, 6, 10-11, 13, 14 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Yee et al.

Applicants and Yee et al. (Cited by applicants, PNAS, Vol. 91, 1994, pp. 9564-9568, see whole article, particularly the Abstract, "Results" section (paragraphs 1, 5-6) and "Discussion" section) recite a genetic construct comprising a gene of interest operably linked to a retroviral vector carrier comprising a VSV transmembrane glycoprotein expressed on the surface of the carrier. Applicants and Yee et al. also recite a method of targeting a gene to a cell (hepatocytes) comprising administering said genetic construct to a cell *ex vivo*. Yee et al. therefore teaches the claimed invention.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

Claims 1-3, 5, 8 and 10-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Schreier et al.

Applicants and Schreier et al. (U.S. Patent 5,753,258, issued 5/19/98, filed 10/8/93, see whole document, particularly column 2, lines 3-6; column 4, lines 27-32, column 6, lines 46-column 7, lines 1-20; column 8, lines 23-31 and claims 1-5, 18) both recite a genetic construct comprising a gene operatively linked to a non-biologic carrier

(proteoliposome) wherein the carrier is associated with a viral (Ebola) transmembrane glycoprotein which is expressed on the surface of the carrier. Applicants and Schreier et al. both recite a method for targeting a gene to a cell comprising administering the genetic construct and carrier to the target cell *in vivo* or *ex vivo*. Schreier et al. therefore teaches the claimed invention.

Claims 1-2, 4-8, 10-11, 13-15 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Kraus et al.

Applicants' invention is as described above. Additionally, in claim 7 the viral vector is recited as being a lentiviral vector and claims 15 and 20 recite administration of the vector to cells *in vivo* or *ex vivo* followed by administration to a patient. Kraus et al. (U.S. Patent 6,235,881, issued 5/22/01, effective filing date of 7/26/95, see whole document, particularly columns 25-30 and Example 11) recites lentiviral vectors pseudotyped with VSV G glycoprotein and methods of targeting a gene to a cell comprising administering the vector (which can be in a liposome) to a cell *in vivo* or *ex vivo* and administering the cells to a subject. Kraus et al. therefore teaches the claimed invention.

Claims 1-2, 4, 10-11, 13-17 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Cohen-Haguenauer et al.

Applicants invention is as recited above. Cohen-Haguenauer et al. (U.S. Patent 6,432,709, issue 8/13/02, filed 11/30/95, see whole document, particularly column 7, 9-

10 and 18-19) recites the generation of pseudotyped retroviral vectors comprising a viral transmembrane glycoprotein (env protein) and methods of infecting hepatocytes and endothelial cells comprising administering the vector to the cells *in vivo* or *ex vivo* followed by introduction of the cells into a subject. Cohen-Haguenauer et al. therefore teaches the claimed invention.

Claims 1-2, 4-5, 8, 10-11, 13-16 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Bodner et al.

Applicants' invention is as described above. Also, claim 18 recites a method of targeting a gene to a monocyte. Bodner et al. (U.S. Patent 5,681,746, issued 10/28/97, filed 12/30/94, see whole document, particularly the Abstract, columns 3, 5 and 18-20) recites pseudotyped retroviral vectors comprising a viral transmembrane glycoprotein and methods of infecting monocytes and endothelial cells comprising administering the vector (with or without liposomes) to the cells *in vivo* or *ex vivo*. Bodner et al. therefore teaches the claimed invention.

Claims 1-2, 4-6, 8, 10-11, 13-15, 19 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Rooney et al.

Applicants' invention is as described above. Claim 19 recites a method of targeting a gene to a dendritic cell. Rooney et al. (U.S. Patent 5,962,318, issued 10/5/99, filed 11/15/96, see whole document, particularly columns 7 and 15-18) recites retroviral vectors comprising a transmembrane glycoprotein (env protein) and methods

of targeting a gene to a dendritic cell *ex vivo* or *in vivo* comprising administering the vectors (with or without liposomes) to the cells. Rooney et al. therefore teaches the claimed invention.

Claims 1-2, 4-6, 8-11, 13-14, 17, and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Levine et al.

Applicants' invention is as recited above. In addition, Claim 9 recites the claimed genetic construct wherein the carrier is a DNA-protein complex. Levine et al. (U.S. Patent 5,723,333, issued 3/3/98, filed 7/31/95, see whole document, particularly column 5, lines 25-66; paragraph bridging columns 8-9; column 14, lines 52-60) recites retroviral vectors or DNA-protein complexes or viral envelope/capsid-DNA complexes comprising a transmembrane glycoprotein expressed on the cell surface and methods of targeting a gene to a cell (i.e. a hepatocyte) comprising administering the vectors or DNA-protein complexes (with or without liposomes) to the cells. Levine et al. therefore teaches the claimed invention. Levine therefore teaches the claimed invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim methods of targeting a gene to a cell comprising administering the claimed genetic construct and carrier associated with a transmembrane form of a viral glycoprotein (such as ebola glycoprotein) to said cells. The only disclosed use for said methods is *in vivo* or *ex vivo* gene therapy or immunization (see p. 5 of the specification). The claimed methods will therefore be evaluated as gene therapy or immunization claims based upon the only disclosed use of said methods.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter.1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and they include the following:

1) Unpredictability of the art. The art in the area of gene therapy and immunization using recombinant vectors and constructs is highly unpredictable. With regard to gene therapy, unpredictability is manifested in virtually every level, from production of the vectors in usable quantities, to inefficient delivery of the transgenes to the target cells to unpredictable and transient expression of the transgenes in cells in vivo. The unpredictability in attempting to treat any given disease in humans is

augmented by the lack of suitable animal models for most disease conditions in humans and the unpredictability in attempting to reproduce in humans the results obtained in the few animal models that do exist (for example Fox (Nature Biotechnology, Vol. 18, 2000, pp. 143-144) notes that one of the most commonly utilized and well studied gene therapy vectors (adenoviral vectors) behaved very differently in human trials compared with their behavior in animals). With regard to *ex vivo* gene therapy, Verma et al. (see below) notes that transgene expression becomes transient and unpredictable once transduced cells are reintroduced into subjects. Also, with regard to attempting to direct or re-direct the specificity of gene therapy vectors, Paillard (Human Gene Therapy, Vol. 9, 1998, pp. 767-768) notes that although the concept appears attractive, many significant problems need to be overcome in order to make the concept of directing or re-directing the specificity of vectors usable in gene therapy. Paillard indicates that development of chimeric envelopes will have to be considered on a case by case basis. For reviews on the unpredictability of gene therapy please see Kmiec, American Scientist, Vol. 87, 1999, pp.240-247; Anderson, Nature, Vol. 392, 1998, pp. 25-30; Verma et al., Nature, Vol. 389, 1997, pp. 239-242).

With regard to recombinant vaccines or immunizing agents targeted to specific cells or tissues, the art is highly unpredictable. With regard to using recombinant vectors or other delivery vehicles to immunize hosts against diseases, it is unpredictable whether the vector or other carrier comprising the transmembrane protein will present the foreign protein to the host immune system in a manner sufficient to raise a protective humoral and/or cell mediated immune response. For example, if the claimed

genetic constructs and carriers are designed to deliver a gene encoding a HIV protein (such as tat) and are to be used in a method of immunizing a subject against HIV infection, it is unclear if the infected or transduced cells can present the HIV protein to the immune system in a manner sufficient to provide protection against HIV infection. Likewise, if the genetic construct-carrier immunizing agent is directed against a pathogen such as HCV or poliovirus, which is restricted to specific tissues in the body, it is unclear if the genetic construct-carrier can elicit the proper immune response against the pathogen in the tissues affected by the pathogen. With regard to attempts to generate vaccines against pathogens such as HIV HCV, malaria, etc., Cohen (Science, 1994, Vol. 265, pp. 1371-1373) recites Jonas Salk as saying that scientists researching vaccine development "don't have a clue" as to what is required to make an effective vaccine and that "There's going to be a need for more awareness not of the pathogen, but of the host." For reviews of the unpredictability involved in use of recombinant vaccines, see Sprent et al., Science, 1994, Vol. 265, pp. 1395-1399 and Rabinovich et al., Science, 1994, Vol. 265, pp. 1401-1404, etc. Also, given that the instant claims are broad (reading on methods of immunizing against any pathogen), given that different pathogens have different strategies for evading the host immune system (See Oldstone, Virology, 1997, Vol. 234, pp. 179-185), given that many pathogens avoid the host immune system by residing at sites in the body that are relatively inaccessible to conventional treatment or vaccines (i.e. HIV which persists in lymph nodes) and given that many pathogens can present different antigens to the host immune system over time (i.e. HIV, malaria, trypanosomes, etc.), the skilled artisan would conclude that it

would be unpredictable as to whether the administration of the claimed genetic constructs-carriers would be effective immunizing agents against any given disease.

2) State of the art. The state of the art with regard to gene therapy and immunization using recombinant genetic constructs-carriers is poorly developed. At the time of applicants' invention no successful gene therapy protocol had been unambiguously demonstrated. Likewise, no successful method of vaccinating humans against any disease using recombinant vectors comprising carriers containing glycoproteins capable of targeting the construct to specific cells had been demonstrated.

3) Number of working examples. Applicants present no working examples of the claimed invention.

4) Amount of guidance provided. Applicants provide no specific teachings on use of the claimed invention to treat any specific disease or immunize against any given pathogen. Applicants only provide generic teachings on general methods of administering any given pharmaceutical agent.

5) Scope of the invention. The scope of the invention is broad, reading on gene therapy for any disease and immunization against any pathogen.

6) Nature of the invention. The invention involves some of the most complex areas of molecular biology-medicine, gene therapy and immunization using recombinant genetic constructs.

7) Level of skill in the art. The level of skill in the art is high; however, given the unpredictability of the art, the broad scope of the claims, the poorly developed state of

the art and the lack of guidance provided by applicants, it must be considered that the skilled artisan would have needed to conduct undue and excessive experimentation in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have needed to practice undue and excessive experimentation in order to practice the claimed invention.

It is noted that claims 10-20 are rejected under art and enablement. This is not inconsistent in this case because the art teaches the method steps recited by applicants and is therefore applicable. However, since applicants' specification discloses that the only contemplated use of the recited methods is for gene therapy or immunization, enablement issues concerning gene therapy and immunization must be considered.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 and10-12 (and dependent claims) are vague in the recitation of the phrase "viral glycoprotein or derivative thereof" because it is unclear what the term "derivative thereof" encompasses. How closely related to the starting glycoprotein does

the derivative need to be in order to be termed a derivative? The specification provides no guidance or teaching on how this term is to be defined. The metes and bounds of the claimed subject matter are unclear.

Claims 1 and 10 are vague in the recitation of the phrase "gene operatively-linked to a carrier" because it is unclear how the gene is linked to the carrier. Applicants' specification defines "operatively-linked" as referring to "functional linkage between a nucleic acid expression control sequence (i.e., gene), wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence." It is unclear how this definition of "operatively–linked" relates to "a gene operatively-linked to a carrier".

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Faxes may be sent directly to the examiner at (703) 746-5061.

Any inquiry of a general nature or relating to the status of this application or proceeding or relating to attachments to this Office Action should be directed to Patent Analyst Zeta Adams whose telephone number is (703) 305-3291.

David Guzo
September 25, 2002

DAVID GUZO
PRIMARY EXAMINER